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Non-alcoholic fatty liver disease is associated with coronary flow reserve impairment

A pilot meta-analysis

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Abstract

Background: Non-alcoholic fatty liver disease (NAFLD) is estimated to affect approximately 25% of the global population. Both, coronary artery disease and NAFLD are linked to underlying insulin resistance and inflammation as drivers of the disease. Coronary flow reserve parameters, including coronary flow reserve velocity (CFRV), baseline diastolic peak flow velocity (DPFV), and hyperemic DPFV, are noninvasive markers of coronary microvascular circulation. The existing literature contains conflicting findings regarding these parameters in NAFLD patients.

Methods: A comprehensive systematic search was conducted on major electronic databases from inception until May 8, 2024, to identify relevant studies. We pooled the standardized mean differences (SMD) with 95% confidence intervals (CI) using the inverse-variance random-effects model. Statistical significance was set at $P < .05$.

Results: Four studies with 1139 participants (226 with NAFLD and 913 as controls) were included. NAFLD was associated with a significantly lower CFRV (SMD: −0.77; 95% CI: −1.19, −0.36; $P < .0002$) and hyperemic DPFV (SMD: −0.73; 95% CI: −1.03, −0.44; $P < .00001$) than the controls. NAFLD demonstrated a statistically insignificant trend toward a reduction in baseline DPFV (SMD: −0.09; 95% CI: −0.38, 0.19; $P = .52$) compared to healthy controls.

Conclusion: Patients with NAFLD are at a higher risk of coronary microvascular dysfunction, as demonstrated by reduced CFRV and hyperemic DPFV. The presence of abnormal coronary flow reserve in patients with NAFLD provides insights into the higher rates of cardiovascular disease in these patients. Early aggressive targeted interventions for impaired coronary flow reserve in subjects with NAFLD may lead to improvement in clinical outcomes.

Abbreviations: CAD = coronary artery disease, CFR = coronary flow reserve, CT = computed tomography, CVD = cardiovascular disease, ED = endothelial dysfunction, MACE = major adverse cardiovascular events, MRI = magnetic resonance imaging, MS = metabolic syndrome, NAFLD = non-alcoholic fatty liver disease, PET = positron emission tomography, TTDE = transthoracic Doppler echocardiography.

Keywords: cardiovascular disease, coronary artery disease, metabolic syndrome, NAFLD, non-alcoholic fatty liver disease

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1. Introduction

Non-alcoholic fatty liver disease (NAFLD) is a widespread condition affecting approximately 28 million people in the United States and up to 25% of the global population.[1] NAFLD is defined as the accumulation of triglycerides in the liver without alcohol consumption and is closely linked to insulin resistance and metabolic syndrome (MS).[2,3] Recent studies have reported an elevated risk of coronary artery disease (CAD) in NAFLD patients independent of the presence of MS.[4] NAFLD is considered indicative of MS, which precedes cardiovascular diseases such as CAD and stroke.[5–7]

Cardiovascular disease is the leading cause of death in NAFLD patients.[8,9] Early endothelial dysfunction in NAFLD affects the arterial endothelium, which is crucial for atherosclerosis progression.[10,11] This may hinder hyperemic stimulation of coronary blood flow, contributing to a 1.5 times higher risk of coronary microvascular dysfunction in individuals with NAFLD than in those without NAFLD.[12,13]

Given the elevated risk of microvascular dysfunction, it is crucial to assess the coronary artery function in NAFLD. Evaluating coronary microvascular function through coronary flow reserve (CFR), which compares stress to resting myocardial blood flow, delineates both epicardial and microvascular myocardial perfusion.[14] Reduced CFR is a strong predictor of future major adverse cardiovascular events (MACE).[15,16] Numerous studies have demonstrated reductions in CFR in various high-risk clinical conditions including diabetes, hypertension, dyslipidemia, and extracardiac atherosclerotic changes.[17–22] Interestingly, although the presence of NAFLD does not directly correlate with MACE outcomes, it increases the likelihood of CFR dropping below 2.0 to 8.7 times.[13,23] Understanding the association between NAFLD and CFR is critical for early detection and management of cardiovascular risk in affected individuals. To date, limited evidence is available regarding the CFR variations in NAFLD. Hence, we conducted a pilot systematic review and meta-analysis of the CFR in patients with NAFLD.

2. Material and methods

This systematic review and meta-analysis was conducted according to the guidelines set forth by the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) 2020.[24] The PRISMA 2020 Checklist for this systematic review is available as supplementary file (Table S1, Supplemental Digital Content, http://links.lww.com/MD/N482). This systematic review protocol was prospectively registered in the International PROSPERO Registry (CRD42024547655).

2.1. Search strategy

A comprehensive literature search was performed using the MEDLINE (via PubMed), Embase, Cochrane Library, Google Scholar, Scopus, and clinicaltrials.gov databases from inception until June 2024. We employed various search keywords and medical subject headings (MeSH) terms such as: "non-alcoholic fatty liver disease," "NAFLD," "Non-alcoholic steatohepat*," "coronary flow," "coronary flow reserve," and "diastolic peak flow velocity." The search strategy was edited and modified according to database requirements (Table S2, Supplemental Digital Content, http://links.lww.com/MD/N482). The search was performed to identify studies evaluating the CFR between patients with NAFLD and healthy controls. All database searches were conducted without imposing any restrictions on publication year or language. To ensure exhaustion and completeness, the reference lists were manually screened to identify relevant articles.

2.2. Study selection and eligibility criteria

The inclusion criteria were as follows: population, intervention, control, and outcome (PICO) format. In this systematic review framework, "P" represented NAFLD patients, "I" was CFR measurement, "C" denoted healthy controls, and "O" represented outcomes, which were coronary flow velocity reserve, baseline diastolic peak flow velocity, and hyperemic diastolic peak flow velocity. Studies that reported at least 1 outcome of interest were included.

Exclusion criteria:

(1) Studies were excluded if they were reviews, case reports, viewpoints, letters to the editors, or study protocols.
(2) Studies were excluded if they did not have a control group to compare the outcomes with NAFLD cases.
(3) Animal models and in vivo studies.

All articles retrieved by the database search were imported into EndNote software (Clarivate Analytics, Philadelphia) and underwent duplicate removal. Preliminary screening of titles and abstracts was conducted by 2 investigators (H.J. and N.P.). Any disagreements between investigators were resolved by consensus discussion or by consulting a third investigator (R.M.O.).

2.3. Data extraction and quality assessment

The following data were extracted from the final studies: first author name, year, country, study design, number of participants, mean age, male sex (%), diagnostic imaging modality, comorbidities (%), and outcomes of interest. For quality appraisal, the Newcastle–Ottawa Scale (NOS) was used.[25] The NOS evaluates bias as low (≥7 points), moderate (4–6 points), or high (≤3 points). Two independent investigators (F.A.R. and N.P.) completed the assessment.

2.4. Data synthesis and extraction

The extracted data for the meta-analysis were analyzed using Review Manager software Version 5.4 (Nordic Cochrane Collaboration, Denmark) by 2 investigators (H.J. and J.J.). The standardized mean differences (SMD) with a 95% confidence interval (CI) between patients with NAFLD and healthy controls were pooled for all outcomes. Generic variance random-effects models were utilized for continuous outcomes, with a P value < .05, which was considered significant. Statistical significance was considered if the 2-tailed P value was <.05 and if the 95% CI value did not cross the value "1." To evaluate heterogeneity, the Higgins I^2 statistic was used, where <25% indicated low, 25–75% indicated moderate heterogeneity, and >75% indicated high statistical heterogeneity.[26] To address high heterogeneity, a sensitivity analysis utilizing the leave-one-out method was conducted to identify the study that contributed the most to heterogeneity.[27] We also conducted subgroup analyses by dividing studies based on the type of diagnostic modality used to measure coronary flow parameters, that is echocardiography and computed tomography (CT)/magnetic resonance imaging (MRI). Funnel plot visualization was performed for publication bias assessment.

3. Results

Using the aforementioned search strategy, 36 publications were identified from the 6 bibliographic databases. Following the removal of duplicates (n = 15), 21 articles were subjected to preliminary screening of titles and abstracts. Fifteen articles were excluded during preliminary screening. The remaining 6 articles were subjected to a full-text assessment, during which 2 were excluded due to incorrect outcomes (n = 1) or wrong study design (n = 1). Finally, 4 articles were included in the

Table 1

Baseline characteristics of the included studies.

Author name, Year	Country	Study design	Study population	Number of participants		Male (%)		Diagnostic imaging modality	DM (%)		HTN (%)		Dyslipidemia (%)		Metabolic syndrome (%)	
				I	C	I	C		I	C	I	C	I	C	I	C
Yilmaz et al 2010[23]	Turkey	Cross-sectional	NAFLD patients who were seen at out-patient clinics for 12 mo	59	77	46	40	TTDE	27.1	0	NR	NR	NR	NR	23.7	0
Nakamori et al 2012[28]	Japan	Retrospective	NAFLD patients	18	47	56	66	Stress and rest perfusion MRI	28	11	78	64	28	28	NR	NR
Pinarbasi et al 2012[29]	Turkey	Prospective	NAFLD patients	24	28	46	61	TTDE	NR	NR	NR	NR	NR	NR	NR	NR
Vita et al 2019[13]	USA	Retrospective	NAFLD patients who were suspected of CAD	125	761	28	29	Quantitative MPI with PET/CT	48.8	26.7	80.8	70.8	62.4	58.9	NR	NR

C = control patients, CAD = coronary artery disease, CT = computed tomography, DM = diabetes mellitus, HTN = hypertension, I = intervention (NAFLD patients), MPI = myocardial perfusion imaging, NAFLD = non-alcoholic fatty liver disease, PET = positron emission tomography, TTDE = transthoracic Doppler harmonic echocardiography.

final meta-analysis.[13,23,28,29] The PRISMA flowchart depicts the comprehensive study selection and screening procedure (Fig. S1, Supplemental Digital Content, http://links.lww.com/MD/N482).

3.1. Baseline characteristics of included studies

This meta-analysis 4 included studies that were conducted between 2010 and 2019, with 1139 participants in total. Of the included studies, 2 were conducted in Turkey,[23,29] 1 in Japan,[28] and 1 in the United States.[13] Detailed baseline characteristics and comorbidities are presented in Table 1. The inclusion and exclusion criteria for the studies included in this meta-analysis are listed in Table S3, Supplemental Digital Content, http://links.lww.com/MD/N482.

3.2. Outcomes

3.2.1. Coronary flow velocity reserve. Data on coronary flow velocity reserve was reported in all included studies.[13,23,28,29] NAFLD was associated with a statistically significant reduction in coronary flow velocity reserve compared with healthy controls (SMD: −0.77; 95% CI: −1.19, −0.36; $P = .0002$; $I^2 = 78\%$; Fig. 1A). On sensitivity analysis to address high heterogeneity, omitting Vita 2019 reduced I^2 to 52%. On subgroup analysis based on diagnostic imaging modality, both echocardiography-based and CT/MRI-based studies demonstrated significant reductions in coronary flow velocity reserves (Fig. S2, Supplemental Digital Content, http://links.lww.com/MD/N482).

3.2.2. Baseline diastolic peak flow velocity. Data on baseline diastolic peak flow velocity were reported in 2 studies.[23,29] NAFLD was associated with an insignificant trend toward reduction in the baseline diastolic peak flow velocity compared to healthy controls (SMD: −0.09; 95% CI: −0.38, 0.19; $P = .52$; $I^2 = 0\%$; Fig. 1B). In subgroup analysis based on diagnostic imaging modality, data on baseline diastolic peak flow velocity were reported only by echocardiography-based studies (Fig. S3, Supplemental Digital Content, http://links.lww.com/MD/N482).

3.2.3. Hyperemic diastolic peak flow velocity. Data on hyperemic diastolic peak flow velocity were reported in 2 studies.[23,29] A statistically significant reduction in the hyperemic diastolic peak flow velocity was noted in NAFLD subjects compared to healthy controls (SMD: −0.73; 95% CI: −1.03, −0.44; $P < .00001$; $I^2 = 0\%$; Fig. 1C). In subgroup analysis based on diagnostic imaging modality, data on hyperemic diastolic peak flow velocity were reported only by echocardiography-based studies (Fig. S4, Supplemental Digital Content, http://links.lww.com/MD/N482).

3.3. Quality assessment and publication bias

All studies were deemed to be of "good" quality using the Newcastle–Ottawa Scale (Table S4, Supplemental Digital Content, http://links.lww.com/MD/N482). A "low" risk of publication bias in funnel plot visualization was noted (Figs S5–S7, http://links.lww.com/MD/N482).

4. Discussion

To the best of our knowledge, this is the first meta-analysis to evaluate the coronary flow parameters in patients with NAFLD. This meta-analysis demonstrated a blunted CFR in terms of reduced coronary flow velocity reserve and reduced hyperemic diastolic peak flow velocity in NAFLD subjects compared to healthy controls. The baseline diastolic peak flow velocity was comparable between the 2 groups.

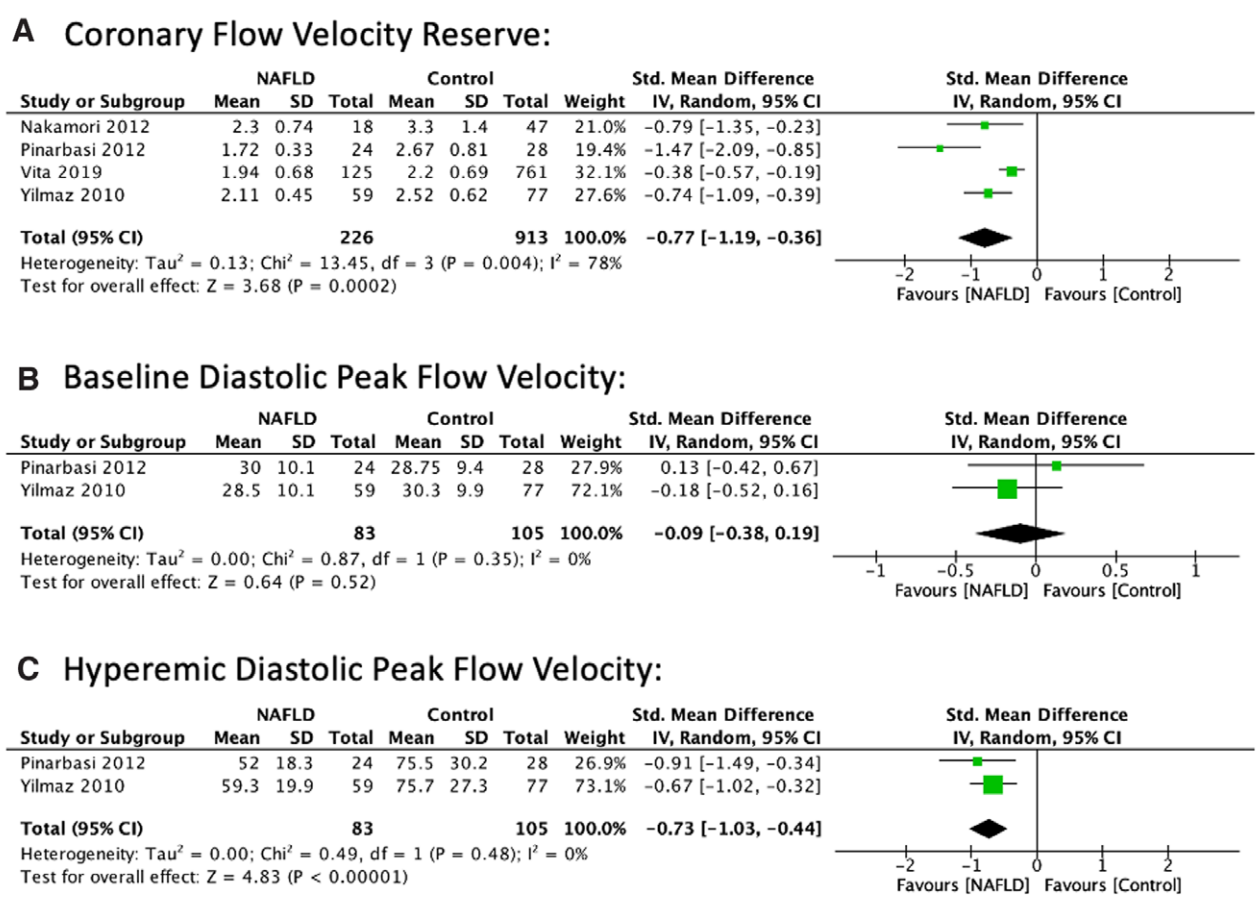

Figure 1. Individual and pooled analyses comparing coronary flow parameters in patients with non-alcoholic fatty liver disease (NAFLD) with healthy controls. (A) Coronary flow velocity reserve; (B) baseline diastolic peak flow velocity; (C) hyperemic diastolic peak flow velocity.

Cardiovascular disease (CVD) is a major cause of mortality in patients with NAFLD, a disease considered for a long time as benign with unappreciated clinical significance.[30–32] Our study aimed to focus specifically on myocardial perfusion measured as CFR and diastolic peak flow velocity in patients with NAFLD to provide mechanistic insights into the development and manifestation of CVD risk in this patient cohort. NAFLD is associated with a higher likelihood of both classical CVD risk factors and CVD events.[33–35] Despite several studies aiming to provide a mechanistic explanation and causality basis of independent potential CVD risk in NAFLD, the evidence is still conflicting, perhaps due to the lack of a reference standard noninvasive diagnostic test for NAFLD.[32,36–38] Several methods are currently used to diagnose this condition, ranging from imaging including ultrasonography, CT, and MRI to liver biopsy and estimation of liver enzymes depending on the center, which partly explains the high heterogeneity of the result of pooling the CFR from the included 4 studies.[39] Additionally, studies have demonstrated a higher chance of left ventricular dysfunction and an increase in left ventricular mass in these patients.[40,41] Only a few studies have focused on the atherosclerotic component of CVD (ASCVD), a leading cause of mortality in these patients.[42] Attempts have been made to examine whether NAFLD is a significant independent risk factor for CAD. In contrast, NAFLD is consistently associated with insulin resistance and metabolic syndrome (MetS).[43,44] MetS is a well-known precursor of CVD, and NAFLD is considered to be a hepatic manifestation of MetS.[45–47] Therefore, insulin resistance and inflammation are common links in the pathogenesis of NAFLD and ASCVD. The exact pathophysiological mechanism by which NAFLD promotes atherosclerosis is still not clear, but these mechanisms linking NAFLD with coronary vascular diseases are at least partly mediated by the atherogenic abnormalities of MetS, such as hyperglycemia, hypertriglyceridemia, and low HDL cholesterol.[48] Atherosclerosis is associated with endothelial dysfunction (ED) in the early stages of the disease process, and NAFLD has been shown to be a risk factor for ED in studies evaluating brachial artery flow-mediated vasodilation.[49] However, data from flow-mediated dilatation of the brachial artery cannot be automatically extrapolated to coronary circulation.[50] In addition to ED as a measure of early atherosclerosis, carotid intima thickness has been shown to be associated with NAFLD.[51–54]. The severity of liver histology has also been shown to correlate with early carotid atherosclerosis[55].

One method of characterizing the state of coronary perfusion impairment due to flow-limiting CAD is to examine CFR. CFR, defined as the ratio of stimulated coronary blood flow velocity to resting value (baseline), assesses epicardial coronary arteries and the integrity of the coronary microvascular circulation and is therefore an indicator of coronary microvascular hypoperfusion.[56,57] Several MRI-based methods have been utilized to measure coronary flow, such as first-pass contrast-enhanced MRI, stress-rest perfusion MRI, and transthoracic Doppler echocardiography (TTDE).[16,58–60] Stress-rest perfusion MRI provides a more objective evaluation of altered CFR in subjects with flow-limiting CAD and microcirculation dysfunction in patients without flow-limiting epicardial coronary artery stenosis, through quantitative evaluation of myocardial blood flow and analysis of the myocardial and blood signal intensity time curves.[61,62] Reduced CFR on quantitative myocardial perfusion imaging with positron emission tomography (PET)/CT is a powerful risk marker for MACE.[15] TTDE is a cheap,

noninvasive, and repeatable method for evaluating the structural and functional status of the epicardial coronary arteries, and has attracted attention as a tool for the accurate determination of reduced CFR.[16,63] An altered CFR has been reported in different cohorts at increased cardiac risk including patients with hypertension, diabetes mellitus, dyslipidemia, hemodialysis patients as well as in patients with extracardiac atherosclerotic changes.[17–20,64] For instance, reduced CFR in patients with hypertension can be attributed to higher myocardial oxygen consumption and reduced coronary microvascular beds in the presence of LV hypertrophy.[65,66] A noteworthy role that merits discussion is the hepatic fat content. Lautamäki et al[67] showed higher hepatic fat content as an independent predictor of myocardial insulin resistance and lower coronary microvascular vasodilator capacity in patients with diabetes mellitus by using 15-oxygen water PET to measure CFR. They quantified the extent of hepatic steatosis using MR proton spectroscopy and found that patients with higher liver fat content had higher levels of myocardial insulin resistance, lower myocardial glucose extraction rates, and lower CFR; however, this has not been sufficiently evaluated for NAFLD (with or without coronary stenosis).

Vita et al[13] was the largest study to demonstrate the hypothesis that coronary microvascular dysfunction can explain the higher risk of MACE in patients with NAFLD where CFR provided a strong cardiac prognostication to CVD events. Vita et al also observed that although NAFLD is predictive of microvascular dysfunction, it was not consistent with MACE or all-cause mortality. This observation was in line with another study by Shah et al[68], who did not find any association between hepatic fat content and overall cardiovascular events or mortality; however, they reported that patients with hepatic steatosis were more likely to have features of adverse left ventricular remodeling. It is therefore possible that pathways involved in liver fibrosis, such as subclinical inflammation, increased oxidative stress, an abnormal adipocytokine profile, and lipid abnormalities, could contribute to ED and, thus, to an impairment in CFR.[69] Inflammatory or oxidative stress is a proposed mechanism linking fatty liver and atherosclerosis. Systemic inflammation has been linked to both fatty liver and CAD, and Nakamori et al found that C-reactive protein level differed between the 2 groups and was moderately associated with liver minus spleen attenuation.[28,70] Increased ROS production of reactive oxygen species is thought to be 1 of the key events in the pathogenesis of ED.[71] Theoretically, therefore, ED should be worse in non-alcoholic steatohepatitis type NAFLD than in non-alcoholic fatty liver, although Ahishali et al[72] found that mitochondrial function, an important determinant of oxidative stress in the 2 NAFLD groups, was comparable. Regarding the role of lipid abnormalities, particularly hypertriglyceridemia, myocardial vasodilatation was reduced in patients with hypertriglyceridemia without overt coronary stenosis.[73] Adipokine may participate in modulating coronary circulation, and hypoadiponectinemia, which is suggestive of advanced fibrosis, has been identified as a possible risk factor for impaired CFR in women.[74–76] Vasoactive molecules such as angiotensin and endothelin may also play important roles in fibrotic liver diseases.[77]

Our results suggest that coronary microvascular dysfunction could explain the increased cardiovascular risk and increased atherosclerotic changes observed in patients with NAFLD. A lower CFR is correlated with a higher incidence of MACE. Timely risk stratification for CVDs in patients with NAFLD could also assist in patient-centered clinical decision-making.[78–80] Characterization and assessment of associated risk factors and morbidities that elevate cardiovascular mortality, such as diabetes, smoking, and obesity coexisting with NAFLD, could provide personalized risk assessment and treatment plans. The current risk stratification tools available for NAFLD should incorporate the presence of abnormal CFR, as they have exceeding clinical relevance. This meta-analysis demonstrated altered coronary flow parameters in a patient population without overt cardiovascular diseases. Hence, early detection of abnormal coronary flow using advanced imaging tools should be offered to patients with NAFLD, particularly those with associated risk factors.[81]

4.1. Limitations

Despite being a pilot meta-analysis, our results must be interpreted after acknowledging several limitations. First, it is important to note that all studies on this topic are observational and no randomized prospective studies are available. This could be attributed to obstacles in conducting randomized controlled research on this topic, most likely due to ethical considerations. Second, observational studies are hypothesis generating with multiple inherent limitations, such as confounders and between-study heterogeneity. Data from randomized studies can eliminate these inherent biases and provide more comprehensive insights. Third, although this meta-analysis reported no heterogeneity in most outcomes, 1 outcome had high heterogeneity, which warranted a sensitivity analysis. This can be partly attributed to the variability in the methods of diagnosing NAFLD and partly to the variability in measuring CFR. Fourth, baseline variations in the included study population could not be adjusted, which introduces limitations to the generalizability of the results. Fifth, the small number of studies included in this meta-analysis restricts further subgroup analysis and publication bias analysis using regression tests. Lastly, the sample size of this study, with only 226 NAFLD patients, warrants careful extrapolation. This is attributed to the lack of studies in this area. Nevertheless, this study supports the available evidence and provides a basis for future research with a larger sample size, preferably with randomized designs, to strengthen the evidence.

5. Conclusion

NAFLD is associated with a blunted CFR, as measured by a reduction in coronary flow velocity reserve and hyperemic diastolic peak flow velocity. No significant difference in the baseline diastolic peak flow velocity was noted in either group. The meta-analysis results and findings are summarized in the graphical abstract (Graphical Abstract, Supplementary Digital Content, http://links.lww.com/MD/N482)). Future research should be conducted with a larger patient population and a randomized study design.

Author contributions

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